fils Gambrié
Nancy:

Some and words on Reps from Africa.
Investing in youth

According to United Nations estimates, the number of young people between the ages of 15 and 24 in North America, Europe and the Soviet Union will slowly decline from 172 million in 1980 to 154 million in the year 2000. But in most of the developing world, the heavy concentration of young people in that age group will continue to increase – in some cases very rapidly. In the Caribbean nearly one-third of the population is aged between 10 and 19, in the Arab World the 15-24 age group has already increased by a quarter in the last five years, and in Africa the numbers in this age group are expected to nearly double by the year 2000.

This is one good reason for attempting to concentrate attention in 1985 on the needs of young people through International Youth Year. The growing cohorts of young people now entering their teenage years will form the parents, workers, leaders and hope of the next century – and they are faced with perhaps the most radical period of change in human history. For many countries it will be the period of the largest absolute population increase and of the greatest movement of people from country to city. It will be a time of sensitive cultural adjustment.

One aspect of that adjustment is the subject of this issue of People: how young people are coping in their personal relationships with their frequently earlier physical and sexual maturity, with changing relations within the family and with outside influences on their behaviour, ranging all the way from the messages of television and advertising to high levels of unemployment and a general trend towards later marriage.

Many young people grow up with little understanding of their bodies and of their emotional responses. The results, both in developed and developing countries, are spelt out in the voices of young people themselves reported in this issue and analysed by our contributors. Some measure of the scale of the problem is given by James Chui who reports on the million unplanned teenage pregnancies occurring last year in the United States, where one teenager in seven has an abortion. From Africa, Anne Jean-Bart, our correspondent in Senegal, reports on one community where 70 per cent of young men have sexual relationships with unmarried girls, but less than half give any support to the children of such liaisons. The disaffection of Arab youth is graphically explained by Fatima Mernissi, who shows how the generation gap has led to extreme reactions among the young. And Tirbani Jagdeo details how, in the Caribbean, the consequences of teenage parenthood, “unlike acne, remain to plague the young throughout adulthood and place them on an endless cycle of diminishing life chances”.

Many of our contributors point to the reluctance of governments to enter these tricky waters, a fact reflected in the relatively low level of international funding for youth programmes. At the same time the role of non-governmental organizations, and of the family planning associations in particular, is clearly of great value. Where governments have made an effort to provide family life and sex education and services to young people valuable progress has been made in lowering the number of teenage pregnancies. In Sweden teenage abortions have been cut by a quarter in just five years.

It is all the more disappointing that the United States should have deprived the International Planned Parenthood Federation of the expected funding of some $17 million in 1985, on the grounds that a few member associations of this federation are doing some abortion work, using non-US funds. One result of this decision – aimed, it appears, at appeasing the anti-abortion lobby in the United States – will be to cut back on much-needed youth programmes around the world, leading to an increase in teenage abortions.

Depo-Provera

Sir, As you reported in People 1985, the British Government approved the injectable Depo-Provera for long-term contraceptive use in April 1984, reversing an earlier prohibition order. This decision must be of crucial interest in Africa, where in the past decade there have been waves of politically inspired adverse comments in the media on the use of Depo-Provera for contraception in Ghana, Nigeria, Kenya and other African countries. It was alleged that because the drug was not used in the United States and some European countries, advocacy of its use in Africa was tantamount to genocide by the imperialists and their agents.

What happened in Ghana was typical. In 1982 there was a series of critical media comments on the use of Depo-Provera. The Medical Advisory Committee of the National Family Planning Programme issued a statement supporting its use, based on scientific evidence of the drug’s safety and its special suitability for the country such as Ghana. The media refused to publish the Committee’s statement and instead continued to publish adverse comments against family planning in general and Depo-Provera in particular.

Soon afterwards, when a drug importer applied for a licence to import Depo-Provera, his application was rejected on the grounds that the drug was prohibited in the UK for contraceptive use. Last April, when the new approval for use of the drug was announced, the officer was asked whether he is now prepared to give a licence for Depo-Provera. He was apologetic and presumably would now be more inclined to allow the importation.

The lessons that may be learned from this story are threefold: firstly, politicians, policy-makers and government officials should consult their national experts on technical issues of family planning before making any pronouncement on scientific aspects of family planning. Secondly, government officials in the developed countries must appreciate the consequences of political decisions on family planning made without scientific backing. Such decisions may be expedient at the time in a particular country but they tend to affect the thinking on family planning in their previous colonies. Thirdly, the media, especially those in Africa, should be advised to avoid sensational reporting on the sensitive subject of family planning, which most African leaders profess to support.

Professor D.A. Ampofo University of Ghana Medical School, Accra.

Mexico City

Sir, It is particularly appropriate that People’s special issue on the International Conference on Population included Lloyd Timberlake’s thorough profile of the situation in Ethiopia. The famine reminds us that the lofty ideals of family planning and sustainable development that run through the World Population Plan of Action will ring hollow unless they are quickly put to the test in Ethiopia, many of her African neighbours, and throughout the world. A balance between human numbers and resources can be restored by falling birth rates or rising death rates – but only one creates a basis for enhanced well-being.

While the press coverage of the Mexico City conference tended to highlight the controversy, People emphasized the underlying consensus that will sustain and expand family planning efforts in the years ahead. A failure to maintain the momentum of public awareness and support that has returned in 1984 will ensure that famine will be an all-too-frequent occurrence as the world’s population grows past 6 billion.

Edward C. Wolf
Worldwatch Institute, Washington DC 20036

Sir, The 1984 International Conference on Population will be remembered as the occasion on which 148 governments agreed that rapid population growth, especially in poor countries, is a serious drag on efforts to achieve socioeconomic development. Also, that there are humane and effective ways to address the problem: expanding the roles and status of women, improving the survival and well-being of children and mothers, increasing user-oriented availability of contraceptives.

It was also agreed that non-governmental organizations are playing centrally important roles and that there is an expanding need for research: the promotion and analysis of useful knowledge. I congratulate People on getting these consensus across in its last issue.

George Zeidenstein
file: Depo-Provera
Nancy:
It's all relative!
There is clear evidence of the risks of pills &
IUDs. They can cause fatal complications.
The pill could cause cancer, i.e. we can't
yet be sure about its
growth & long-term effects & they
are not always worse vs.
cervical cancer. Injectable
are not killed no one &
there's nothing to undermine
they do endanger life.
Scientific panels x 3
have recommended to
have approved IUDs for
U.S. contraception use. But they
contra-argument more. But they
guarantee it's safe.
I'm not sure about
makers of the Board. This is
for you.
Tony's underlining

Did the indiv. experts
advise the public
Board on & make up
its membership?

This is less surprising

than I expected,
though the bottom line
is still, given maternal
mortality risk etc., positive.
Did you want it both ways?
Nancy:

Be the Gambia
& elsewhere, suggest
upon skin the
attacked sometime.

Love
II REPORTS ON INDIVIDUAL DRUGS

This section provides background information on decisions resulting either in withdrawal or restriction in the use of specific products in Member States. For the benefit of countries where access to this information is difficult a short review of relevant published literature is provided.

1. INJECTABLE CONTRACEPTIVES (II)

The efficacy and short term safety of the injectable progestogenic contraceptives, depot medroxyprogesterone acetate (DMPA) and norethisterone enantate (NET-EN), were discussed in the previous issue of this bulletin. However, as is the case with other steroid contraceptives, it is their safety in the longer term that will ultimately determine their future use.

Within the past two years DMPA has been registered for long term contraception, when other methods are inappropriate or unacceptable, in Sweden and the UK, while both DMPA and NET-EN have been accepted for this purpose in the Federal Republic of Germany. In contrast, a Public Board of Inquiry, composed of invited scientific experts, has now advised the US Food and Drug Administration that the available evidence does not provide a sufficient basis for determining that DMPA is safe for general marketing in the USA (1).

In essence, the report of the Public Board of Inquiry is a restatement of a position previously adopted by the FDA. It derives from a formal requirement that all contraceptive drugs must be tested for carcinogenicity in rodents, dogs and monkeys (2) and that any positive findings must, de facto, be regarded as constituting evidence of lack of safety. Other national drug regulatory authorities contest the validity of applying these guidelines to steroid hormones.

It is thus timely to provide a brief account of the considerations at issue, and to review these in the light of epidemiological data generated in countries where injectable contraceptives are currently in use.

Experimental carcinogenicity data

Rats

DMPA is not demonstrably carcinogenic in the rat. NET-EN, however, which is mainly progestogenic in other laboratory animals and in women, is predominantly oestrogenic in rats. Predictably, in this species, it enhances hypophysial prolactin secretion. This, in turn, favours the development of hypophysal and mammary tumours. Given that these tumours are a consequence of oestrogenic activity, and that they have been demonstrated in clear excess only following massive dosage over a major portion of the life span, it has been argued that they are unlikely to have relevance to the contraceptive use of NET-EN (3). Less predictably, the yield of benign and malignant hepatic tumours was also increased among rats receiving NET-EN and another study, in which norethindrone is used as a positive control, is now in hand.

In any event, the vagary of testing the carcinogenicity of steroid compounds in rodents has previously been demonstrated in a series of studies commissioned by the United Kingdom Committee on Safety of Medicines (4). The fortuitous use of animals from more than one breeding colony exposed the existence of important strain-dependent variations in response.

Beagle dogs

Dose-related increases in the incidence of benign and malignant breast tumours, including mixed mammary tumours and adenocarcinomas, have been described in beagle bitches exposed for up to 7 years to the equivalent of 1-25 times the contraceptive dose of DMPA (or 1-40 times this dose of NET-EN) (5-7).
Whether or not the beagle model is appropriate for carcinogenicity screening of progestogens has been a subject of debate for 10 years (8). All progestogens, including progesterone, have been claimed to produce these lesions provided that they are administered over a period of several years by an appropriate route at high enough dosage (6,9,10). Corresponding malignancies have not been induced in rats or monkeys. This has aroused speculation that the basic subcellular mechanisms determining biological responses to progestogens are distinctive in the beagle bitch (10).

Critics sceptical of the relevance of the experimental findings point to the atypical pattern of estrous activity in the dog, and to the unrepresentative hormonal mechanisms controlling these changes (11-13). The beagle differs profoundly from women in its sensitivity to specific progestogens and estrogens (14) and in its metabolic and target-organ responses to these compounds (15). A number of substances that have potent progestogenic effects in women display predominantly estrogenic activity in beagles (15). Among the more apparent discrepancies in response is the capacity of progestogens (unopposed by estrogens) to produce endometrial cystic hyperplasia in beagles to the extent that animals used in toxicological tests are often hysterectomised to obviate pyometra. Other metabolic disturbances that develop among these animals are expressed by anestrus, obesity, anaemia, increased production of growth hormone, acromegaly, impaired carbohydrate metabolism, multiple endocrinopathy, glomerulopathy and thromboses (5-7).

The view of the United Kingdom Committee on Safety of Medicines, which is shared by other drug regulatory authorities within Europe, is that the mammary changes in the beagle cannot be regarded as indicative of a significant hazard to women, and that the use of this model for long-term testing of contraceptive steroids should not be regarded as a mandatory requirement for registration purposes (16).

The FDA Public Board of Inquiry, however, does not make concession to this view. While not contesting the thesis that the potential to induce malignant mammary lesions in the beagle is shared by all progestogenic substances, its report concludes that these lesions cannot be disregarded as possible indicators of risk. It points to a number of similarities in the epidemiological and biological characteristics of malignant mammary neoplasias in the dog and the human including their age specific incidence (17), their relationship to ovarian hormones (18) and their possible common derivation from ductal epithelium (19). Too little is known, it argues, of the mechanisms by which progestogens produce these lesions to justify rejection of the evidence.

Rhesus monkeys

Both nodular mammary lesions (20) and endometrial tumours (20,21) have been identified in female rhesus monkeys injected regularly for periods of up to 10 years with DMPA or NET-EN at up to 50 times the normal contraceptive dose.

The mammary nodules and hyperplastic changes in the ductal epithelium - variously described as benign nodular hyperplasia, precancerous lesions and carcinoma-in-situ (22) - were demonstrated exclusively in several monkeys that received the mid-dose (x10) of DMPA. An expert advisory panel to the UK Licensing Authority has concluded that species differences and the absence of a progressive dose-related effect render these lesions irrelevant to contraceptive use (22). However, the FDA Public Board of Inquiry felt that changes resembling a precancerous human lesion could not be discounted, particularly in light of the apparent resistance of monkeys to agents that induce malignancies in breast tissue of other species (1).

Final autopsy of the high-dosed monkeys revealed that two (of 12) animals in the DMPA study and one (of 12) in the NET-EN study had developed poorly differentiated adenocarcinomas, generally considered to be of endometrial origin (21), although their precise cellular origin is disputed (1,21).

There is broad agreement that these lesions are likely to be drug-related, particularly since spontaneous endometrial tumours in the Rhesus monkey are excessively rare (1). Nonetheless, their relevance to women has been questioned because they occurred only in the atrophic endometrium of high-dosed animals (21). In women, carcinomatous changes rarely develop in an atrophic endometrium, but they have been described (23).
The FDA Public Board of Inquiry stresses, however, that insufficient animals were used to exclude with reasonable confidence the possibility that the experimentally-induced lesions might be induced at lower dosage. It also cites evidence that the Rhesus monkey may be relatively unresponsive to progestogens. Finally, while conceding that progestogens are used clinically in the treatment of hormone-dependent cancers of the endometrium, it considers that there is no basis for excluding the possibility that, like estrogens, progestogens may exert paradoxical effects on the neoplastic process at different dosages (1).

Human Epidemiological Data

Fundamental disparities in the assessment of toxicological evidence among national regulatory authorities are exceptional. Attitudes are preconditioned to some extent in the USA by an earlier FDA conclusion, formulated when an application to register DMPA as a contraceptive was disallowed in 1978, that a significant patient population in need of the drug is lacking in the United States. Caution may also be engendered by awareness that the carcinogenic potential of prenatal exposure to diethylstilbestrol and of postmenopausal estrogen replacement therapy was first identified in patient populations.

In any event, the practical consequence of the recommendations adopted by the FDA Public Board of Inquiry - on the assumption that they will be upheld - is that progestogenic injectable contraceptives cannot be introduced in the USA until such time as direct evidence is generated elsewhere that their long-term use carries no significant carcinogenic hazard. Epidemiological proof of their safety, collected in accordance with recommended guidelines (24), would take many years to assemble. A prospective evaluation now in progress within New Zealand, for instance, will not be completed until 1990; even then, the women most recently recruited into the study will have been followed for only five years.

Much of the earlier published information on the occurrence of hormone-dependent cancer in women who have used either DMPA or NET-EN is uncontrolled, and it relates largely to the consequences of relative short periods of use and follow-up (25-37). None of these data definitively excludes a significant drug-related risk, and two apparently positive findings have attracted particular attention:

Cervical screening of more than 1000 women enrolled in a clinical study of DMPA undertaken in the USA provided an incidence of carcinoma-in-situ 2-3 times greater than expected (26,35). It is likely, however, that known risk factors for carcinomas of the cervix were strongly represented within the group (37). Moreover, half the women with positive cytology had first received DMPA less than 8 months earlier, in which case the changes may well have antedated exposure (38).

Three deaths from breast cancer were reported from Canada among 583 mentally retarded women who had received long-term treatment with DMPA (33). This is some 25 times greater than the expected incidence in a comparable age-cohort in the general population (22). However, other risk factors are evident within this group: not only were many of the women nulliparous, they had also received prolonged treatment with psychoactive drugs and anticonvulsants.

These early data are now placed in more secure perspective by preliminary data obtained from Kenya, Mexico and Thailand within the context of a multinational, hospital-based case control study conducted under the auspices of the World Health Organization. The study is designed to assess the influence of DMPA and other steroid contraceptives on risks of neoplasia, including breast and cervical cancer (39), and this interim analysis is based on a total of some 250 cases of cancer of the breast, 450 cases of invasive cervical cancer, and a larger number of controls. The findings relating to cancer of the breast are consistently reassuring: overall the frequency of the disease was lower among women who had used DMPA (relative risk 0.7; 95% confidence interval 0.4-1.2), and this reduction was greatest among women exposed for more than 36 months and those aged over 30 years at the time of first exposure.

In contrast, the frequency of invasive cervical cancer was slightly increased among women who had received DMPA. Overall, this increase was not significant and no clear trend of increasing risk with duration of use was evident. Nonetheless, the highest relative risk (2.20; 1.15-4.21) was recorded among a small group of women exposed for more than 5
years. A similar estimated increase in risk for invasive cervical cancer has been reported among long-term users of orally administered steroid contraceptives, both within the same WHO Collaborative Study (1.53; 1.11-2.12) (40) and within three other recently-reported prospective studies (41-43).

Cervical cancer is common. In some developing countries it is the most frequent form of cancer in women (44). Even a small increase in risk associated with a drug that is widely used will give rise to substantial numbers of additional cases. Moreover, diagnosis is liable to be delayed when the normal menstrual pattern is disrupted and when routine cytological screening is impracticable. However, it would be premature to conclude that an association with injectable contraceptives has been established, and there is no indication from the epidemiological data as yet assembled that injectables are less safe than combined oral contraceptives.

It still remains possible that confounding factors are responsible for the apparent excess of cervical cancer reported in these various studies. Fortunately, the WHO study is readily adapted and extended to examine the risk of cervical cancer in greater depth. Work is already in hand to include serological tests for herpes and papilloma virus infections – possible risk factors for cervical neoplasia – in subsequent phases of the study, and to analyse separately data on the various histological types of cervical cancer, and on the various types and dosages of estrogens and progestogens currently contained in marketed steroid contraceptive products. High priority is being accorded to these studies and the results will be communicated at the earliest opportunity.

References


16. Committee on Safety of Medicines, United Kingdom, Open communication to WHO, 1979.


34. Cervantes A, Azcona SC, Bribiesca LB et al. Effect of medroxyprogesterone acetate on human endometrium after five or more years of use as a contraceptive (unpublished; cited in reference 1).


2. BETA-ADRENORECEPTOR ANTAGONISTS AND RETROPERITONEAL FIBROSIS

Almost 10 years have elapsed since the oral dosage form of practolol - a cardioselective beta-adrenoreceptor blocking agent - was hurriedly withdrawn from use worldwide (1). Its propensity to invoke a wide range of serious histopathological changes in epithelial structures had remained unrecognized until several hundred patients were affected in the United Kingdom alone because the lesions were totally unanticipated and rarely became evident within the first year of treatment. Nonetheless, the causal relationship was ultimately established beyond all doubt: following the withdrawal of the drug the frequency of newly-detected reactions fell promptly and, within a year, notifications of the eye, ear, skin and mucosal lesions that characterised the so-called "practolol syndrome" (2) had virtually ceased.

This sequence of events, together with occasional case reports of afflicted patients who were subsequently treated with other beta-adrenoreceptor blocking agents without recrudescence of symptoms (3,4), offers circumstantial evidence that the hazard was largely, and perhaps exclusively, associated with practolol. Definitive assurance that its widely-used congeners are devoid of a measure of risk is, however, elusive.

No satisfactory explanation has been advanced to explain why or how practolol exerts adverse effects that have no demonstrable connection with its known physiological properties: nor has any attempt been successful to reproduce these lesions in experimental models. Several strands of evidence point to an immunological derangement with...